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## Original Article

## Cardiovascular magnetic resonance characterization of myocardial and vascular function in rheumatoid arthritis patients

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a multisystem, autoimmune disorder and confers one of the strongest risks for cardiovascular disease (CVD) morbidity and mortality.

**Objective:** To assess myocardial function and vascular stiffness in RA patients with and without cardiovascular risk factors (CVRFs) using cardiovascular magnetic resonance (CMR).

**Methods:** Twenty-three RA patients with no CVRFs (17 female, mean age  $52 \pm 13$  years), 46 RA patients with CVRFs (32 female, mean age  $53 \pm 12$ ), 50 normal controls (32 female, mean age  $50 \pm 11$  years), and 13 controls with CVRFs (7 female, mean age  $55 \pm 7$  years), underwent CMR at 1.5 Tesla, including evaluation of left ventricular (LV) ejection fraction, strain, and vascular elasticity (aortic distensibility [AD] and pulse wave velocity [PWV]). Disease activity and duration were recorded for each patient. Subjects with known symptomatic CVD were excluded.

**Results:** LV volumes, mass, and ejection fraction were similar in the four groups. RA patients with CVRFs showed the greatest abnormality in mid short-axis circumferential systolic strain, peak diastolic strain rate, and vascular indices. RA patients without CVRFs showed a similar degree of vascular dysfunction and deformational abnormality as controls with CVRFs. AD and total PWV correlated with myocardial strain and RA disease activity. On multivariate regression analysis, strain was related to age, RA disease activity, AD, and PWV.

**Conclusion:** CMR demonstrates impaired myocardial deformation and vascular function in asymptomatic RA patients, worse in those with CVRFs. Subclinical cardiovascular abnormalities are frequent and appear to be incremental to those due to traditional CVRFs and likely contribute to the excess CVD in RA.

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## 1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown cause, resulting in a chronic, relapsing, and disabling arthritis that is characterized clinically by painful joints, radiologically by erosions, and pathologically by synovitis with fibrosing pannus and a palisade of inflammatory cells. Extra-articular manifestations commonly occur in genetically predisposed individuals with RA,<sup>1</sup> and the heart and vasculature are frequently involved,

**Abbreviations list:** AA, Ascending aorta; AD, Aortic distensibility; CMR, Cardiovascular magnetic resonance; CVRF, Cardiovascular risk factor; DDA, Distal descending aorta; LV, Left ventricle/ventricular; PDA, Proximal descending aorta; PWV, Pulse wave velocity; RA, Rheumatoid arthritis.

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with no segment of the cardiovascular axis spared, resulting in significant morbidity and mortality.<sup>2</sup> Cardiovascular disease (CVD) accounts for 50–80% of the premature mortality in RA,<sup>3</sup> and a 8–15 year reduction in lifespan.<sup>4</sup> In fact, the risk of CVD, in the form of myocardial infarction, heart failure, and stroke, in RA is higher than that in non-RA patients with traditional CVRFs, including diabetes mellitus,<sup>5</sup> typically occurring in young, female RA patients with no known CVD or CVRFs.<sup>6</sup>

Aortic distensibility (AD) and pulse wave velocity (PWV), acquired using various non-invasive techniques, have been demonstrated to be abnormal in patients with RA.<sup>7,8</sup> As a chronic inflammatory disease, RA also involves the myocardium to cause myocarditis and cardiomyopathy,<sup>9</sup> resulting in increased risk of congestive cardiac failure, with both systolic and diastolic dysfunction.<sup>10,11</sup> Our group has previously reported on focal and diffuse myocardial fibrosis and myocardial inflammation that were related to impairments in peak systolic and diastolic circumferential strain in RA.<sup>12</sup>

Rational planning of health care policy and interventional measures are required to tackle CVD in RA patients. However, several gaps exist in our knowledge, making it difficult to plan interventional strategies and base recommendations. First, the frequency of vascular and myocardial dysfunction in RA patients without known CVD or CVRFs is unknown. Second, the degree to which conventional CVRFs interact with chronic inflammation in RA to result in a specific cardiovascular phenotype is unknown. Therefore, the aims of this study were (1) to assess vascular and myocardial function in RA patients without known CVD or symptoms; (2) to assess the consequence of the interaction of CVRFs and chronic inflammation in RA patients without known CVD, using cardiovascular magnetic resonance (CMR); and (3) to correlate CMR findings to disease activity and chronicity.

## 2. Methods

### 2.1. Study subjects

Subjects with RA and no known CVD ( $n = 69$ ) were recruited from 4 rheumatology centers in the United Kingdom. Inclusion criteria were age greater than 18 years but less than 65 years (to avoid the influence of age-dependent vascular and myocardial changes); diagnosis of RA established independently by the respective clinical team based on the American College of Rheumatology (ACR) 1987 criteria<sup>13</sup> (modified 2010)<sup>14</sup>; and stable on disease-modifying anti-rheumatic drugs (DMARDs) for at least 12 weeks. Patients were excluded from enrolment if they were unable to tolerate CMR; had contraindications to CMR; had non-sinus rhythm on a 12-lead electrocardiogram (ECG); had significantly impaired renal function (estimated glomerular filtration rate  $<30$  ml/min); had impaired liver function (alanine aminotransferase more than twice the upper limit of normal); pregnant female; participated in another research study involving an investigational product in the last 12 weeks before enrolment; and/or were unable to give informed consent. Further, patients with symptomatic CVD were excluded either on the basis of the medical history, abnormal ECG, or prior abnormal coronary angiography. All patients fulfilling the inclusion criteria were invited to participate. The study was approved by the Oxfordshire Research Ethics Committee (Ref. 10/H0606/32), and all subjects gave written informed consent before enrolment. A control group ( $n = 63$ ) that comprised healthy subjects matched for age, sex, ethnicity (self-defined), and CVRFs was studied contemporaneously. The control subjects were healthy volunteers recruited from the community, without prior cardiovascular disease, and who had voluntarily responded to an advert to participate in the study.

### 2.2. Definition of CVRFs

Hypertension was defined as a blood pressure  $>140$  mmHg systolic and  $>90$  mmHg diastolic. Smoking was considered significant as a CVRF. Obesity was defined as body mass index (BMI)  $>30$  kg/m<sup>2</sup>. Diabetes was defined as a random serum glucose of  $>11.1$  mmol/L, a fasting serum glucose  $>7.0$  mmol/L, or a 2-hour postload glucose  $>11.1$  mmol/L during an oral glucose tolerance test following ingestion of 75 g of glucose. Dyslipidemia was defined as an elevated total cholesterol ( $>5.2$  mmol/L), LDL cholesterol ( $>2.6$  mmol/L), triglyceride level ( $>1.7$  mmol/L), or reduced HDL cholesterol level ( $<1.0$  mmol/L).

### 2.3. CMR image acquisition and analysis

#### 2.3.1. Left ventricular cardiac volumes, mass, and function

Ventricular volumes, mass, and function were assessed with CMR using a 1.5-Tesla Avanto MR system (Siemens Healthcare, Erlangen, Germany) with steady-state free precession (SSFP), retrospectively gated imaging, as previously described.<sup>15</sup> Late gadolinium enhancement (LGE) images were acquired with a standard T1-weighted phase-sensitive inversion recovery sequence 8–10 minutes after a 0.15 mmol/kg gadolinium contrast (Gadoterate meglumine—Gd-DOTA, Dotarem, Guerbet LLC, France).

#### 2.3.2. Myocardial tagging

Tagged cines were acquired with an ECG-triggered segmented k-space gradient echo sequence with spatial modulation of magnetization (SPAMM).<sup>16</sup> Three short axes (basal, mid-ventricular, and apical) scans and a single long axis (horizontal) scan were obtained (see Fig. 1A–D).

#### 2.3.3. Aortic pulse wave velocity and distensibility

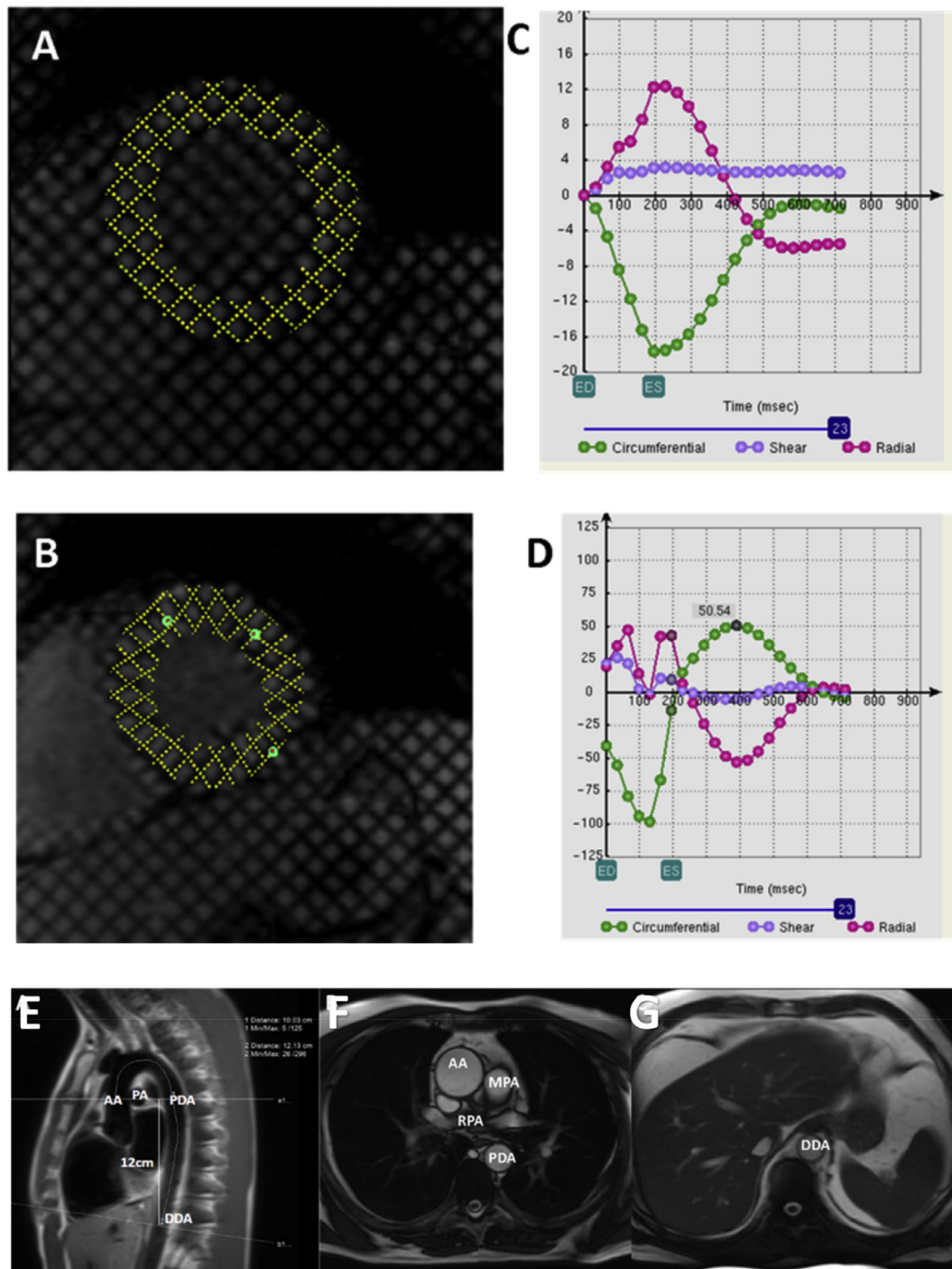
CMR-based aortic PWV was measured using ECG-gated, spoiled gradient echo sequences with velocity-encoding gradient for phase contrast applied to assess through-plane flow in the ascending aorta (AA) and the proximal descending aorta (PDA) at the level of the main pulmonary artery and also in the distal descending aorta (DDA) 12 cm vertically down, just below the diaphragm, perpendicular to the vessel<sup>17</sup> (see Fig. 1E–G).

### 2.4. RA disease activity

Disease activity was assessed using the DAS28-CRP, a disease activity score, which incorporates a 28-tender joint and swollen joint count, in addition to a measure of general health, together with the serum C-reactive protein level.<sup>18</sup> An absolute level of disease activity can be selected as a clinically meaningful goal for therapeutic intervention; with a value of  $\leq 3.2$  defined as the threshold for a low disease activity state and  $<2.6$  as the threshold for remission.

### 2.5. Statistical analysis

Normality of data was tested using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean  $\pm$  standard deviation (SD) or, where highly skewed, as median (interquartile range); discrete data are presented as numbers (percentages). The chi-square test or the Fisher exact test was utilized to compare discrete data, as appropriate. ANOVA with *post hoc* Bonferroni correction was used to explore whether there were differences between the four groups, i.e., RA patients without CVRFs, RA patients with CVRFs, controls without CVRFs, and controls with CVRFs. The Mann–Whitney *U* test was used to compare not normally distributed data between the two groups of



**Fig. 1.** Representative examples of short-axis cine images with myocardial tags in end-diastole and end-systole with systolic strain and diastolic strain rates in a RA patient (A–D) and representative levels of the aorta where aortic distensibility and PWV were assessed (E–G). Cine tagging in a mid short-axis slice in end-diastole (A) and end-systole (B) in a patient with RA and graphs showing peak systolic circumferential strain rate (C) and peak diastolic strain rate (D) in the same patient. E. The ascending aorta (AA) and the proximal descending aorta (PDA) at the level of the pulmonary artery (PA) and in the distal descending aorta (DDA) 12 centimeters vertically down, perpendicular to the vessel; F. High-resolution through-plane flow image acquired at the level of the MPA including the AA and PDA; and G. High-resolution through plane flow at the level of the DDA.

RA patients. Bivariate correlations were assessed using the Pearson “R” and Spearman “R<sub>s</sub>” coefficients, as appropriate. Linear regression analysis of determinants of vascular stiffness and myocardial function was performed. All statistical tests were two-tailed, with p values of less than 0.05 considered statistically significant. Analysis was performed using SPSS version 24 (IBM, Armonk, New York, USA).

### 3. Results

#### 3.1. Baseline characteristics of the study population

RA patients were matched with controls for age, sex, and comorbidities (Table 1). Common DMARDs in RA included methotrexate (~90%), chloroquine (~60%), and sulfasalazine (~25%). RA

**Table 1**  
Baseline characteristics of the study population

	Controls N=50	Controls with CVRFs N=13	RA without CVRFs N=23	RA with CVRFs N=46	P value
Demographic features and co-morbidity					
Female sex	32 (64)	7 (54)	17 (74)	32 (70)	0.61
Age, years	50 ± 11	55 ± 7	52 ± 13	53 ± 12	0.39
Hypertension	0 (0)	4 (31)	0 (0)	12 (26)	–
Diabetes	0 (0)	0 (0)	0 (0)	4 (9)	–
Obesity	0 (0)	6 (46)	0 (0)	14 (30)	–
BMI, kg/m <sup>2</sup>	23 ± 3	28 ± 4	24 ± 2	28 ± 5	<0.001
Medical therapy					
Methotrexate	–	–	21 (91)	39 (85)	–
Chloroquine	–	–	13 (57)	26 (57)	–
Sulfasalazine	–	–	6 (26)	5 (11)	–
Leflunomide	–	–	2 (9)	9 (20)	–
Rituximab	–	–	1 (4)	2 (4)	–
Prednisolone	–	–	1 (4)	7 (15)	–
Duration of DMARDs, years (median ± IQR)	–	–	3 (2–6)	6 (4–9)	–
Duration of NSAIDs, years (median ± IQR)	–	–	2 (1–3)	3 (2–6)	–
Disease activity and chronicity					
DAS28-CRP	–	–	3 ± 1	4 ± 2	–
ESR, mm/h (median ± IQR)	–	–	10 (5–16)	16 (10–24)	–
CRP, mg/L (median ± IQR)	–	–	19 (5–17)	12 (6–16)	–
Duration of RA disease, years (median ± IQR)	–	–	7 (3–10)	10 (7–13)	–

Continuous data are mean ± SD unless otherwise indicated.

Categorical data are frequency (percent) unless otherwise indicated.

AID, autoimmune disease; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; CVRFs, cardiovascular risk factors; DAS28-CRP, rheumatoid arthritis disease activity index, incorporating a 28-joint count and serum CRP; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis.

The p value for female sex is based on the chi-square test, whereas the p values for age and BMI are based on ANOVA analysis.

patients with CVRFs had a longer median duration of RA (10 [7–13] vs. 7 [3–10] years,  $p < 0.001$ ) and had been on DMARDs for longer time (6 [4–9] vs. 3 [2–6] years,  $p < 0.001$ ). Furthermore, RA patients with CVRFs had higher disease activity ( $4 \pm 2$  vs.  $3 \pm 1$ ,  $p = 0.001$ ) when compared to RA patients with no CVRFs.

**Table 2**  
CMR findings

	Controls N=50	Controls with CVRFs N=13	RA without CVRFs N=23	RA with CVRFs N=46	P value
LVEDV, ml/m <sup>2</sup>	77 ± 13	79 ± 16	80 ± 20	75 ± 14	0.45
LVESV, ml/m <sup>2</sup>	22 ± 15	20 ± 6	24 ± 9	21 ± 9	0.56
LVEF, %	74 ± 4	74 ± 3	71 ± 6	73 ± 7	0.22
LV Mass, g/m <sup>2</sup>	53 ± 10	58 ± 12	56 ± 10	54 ± 11	0.21
LA size, mm	26 ± 5	29 ± 5	31 ± 6	32 ± 6	<0.001
Mid SA circumferential strain rate	–19.2 ± 1.0	–18.2 ± 1.2	–17.4 ± 1.3	–16.8 ± 1.1	<0.001
Peak diastolic circumferential strain rate (s-1)	121 ± 12	109 ± 29	82 ± 21	82 ± 20	<0.001
LGE, %	26 (52)	11 (85)	2 (9)	5 (11)	0.002
AA distensibility (10 <sup>-3</sup> mmHg <sup>-1</sup> )	3.5 ± 2.2	2.2 ± 1.4	2.3 ± 1.8	2.0 ± 1.6	0.002
PDA distensibility (10 <sup>-3</sup> mmHg <sup>-1</sup> )	4.2 ± 1.7	3.1 ± 1.5	2.8 ± 1.5	2.6 ± 1.4	<0.001
DDA distensibility (10 <sup>-3</sup> mmHg <sup>-1</sup> )	6.0 ± 2.3	4.4 ± 1.6	4.2 ± 1.9	3.8 ± 2.1	<0.001
Aortic Arch PWV (m/s)	4.4 ± 2.5	5.5 ± 3.2	7.2 ± 4.4	7.7 ± 3.7	<0.001
DDA PWV (m/s)	4.4 ± 2.3	6.0 ± 3.3	6.3 ± 2.9	7.3 ± 3.7	<0.001
Total aortic PWV (m/s)	4.6 ± 2.2	6.0 ± 1.7	6.8 ± 2.7	8.2 ± 3.3	<0.001

Continuous data are mean ± SD unless otherwise indicated.

AA, ascending aorta; CVRFs, cardiovascular risk factors; DDA, distal descending aorta; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle/ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PDA, proximal descending aorta; PWV, pulse wave velocity; SA, short axis; RA, rheumatoid arthritis.

The p values in this table come from separate ANOVAs for the different variables where the ANOVA assumptions were met.

### 3.2. Left ventricular function

These data are presented in Table 2. There were no differences in LV volumes, mass, and ejection fraction between RA patients without CVRFs, RA patients with CVRFs, normal controls, and controls with CVRFs, respectively. However, despite the normal global LV systolic function, there was significant impairment in regional LV systolic and diastolic function in RA patients as assessed by deformation indices (Fig. 1A–D). Midventricular circumferential strain was more markedly reduced in RA patients compared to other groups (Fig. 2A). There was also evidence of impaired diastolic function with peak diastolic circumferential strain rate being most affected in RA patients (Fig. 2B).

### 3.3. Late gadolinium enhancement

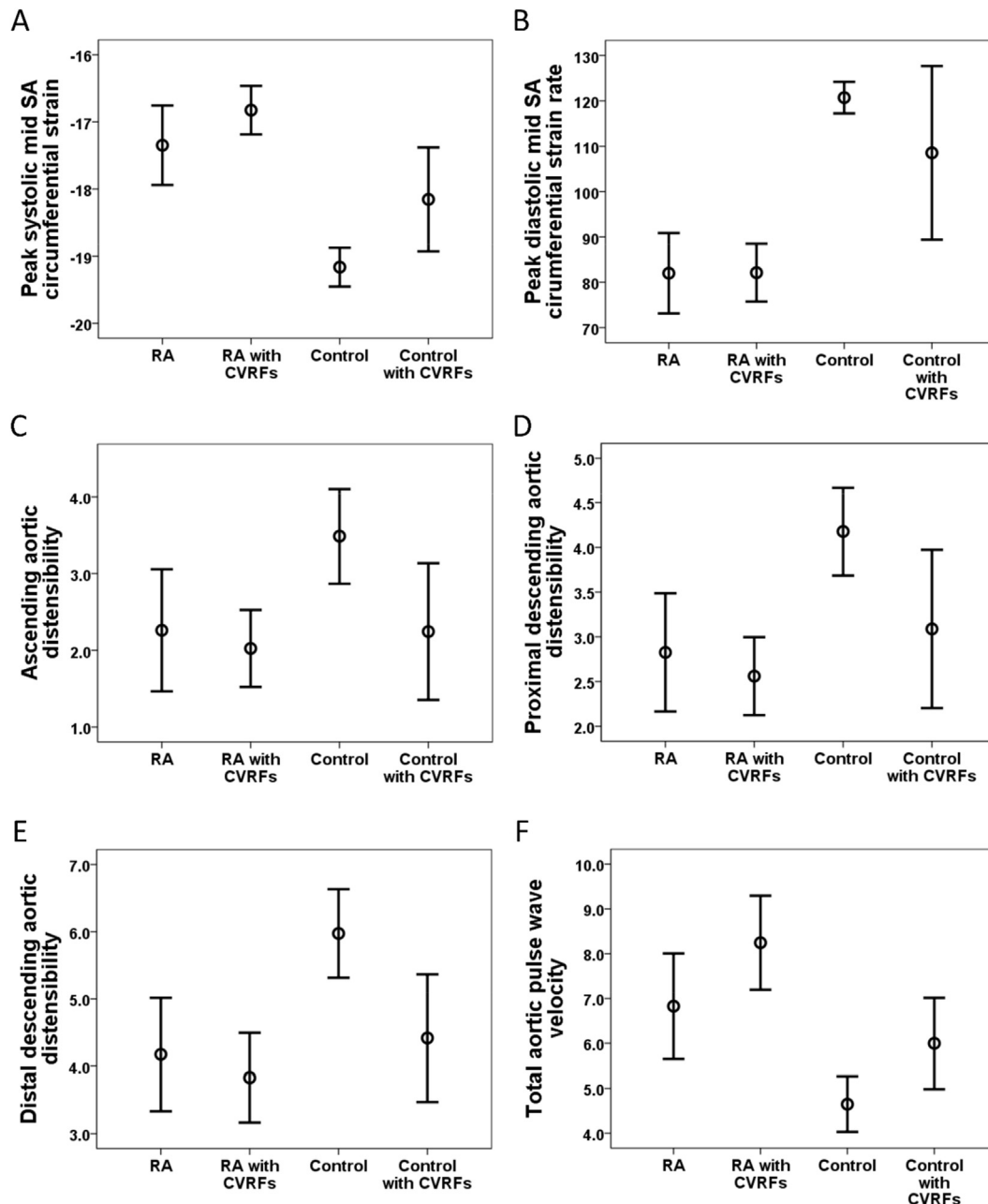
As previously reported,<sup>12</sup> we found increased late gadolinium enhancement in RA patients compared to control subjects (Table 2). LGE was typically patchy and mostly involved the basal to mid inferolateral walls and was more frequent in RA patients with CVRFs.

### 3.4. Vascular function

These data are presented in Table 2. RA patients with CVRFs showed the greatest reduction in AD and greatest increase in PWV at the three different aortic levels (AA, PDA, and DDA), indicating increased arterial stiffness in RA patients, which is worsened by the co-existence of CVRFs (Fig. 2C–F). RA patients without CVRFs had more severe abnormalities in both AD and PWV compared to controls with CVRFs.

### 3.5. Arterial stiffness, myocardial strain, and covariates

There were significant correlations between vascular indices and deformation indices (Fig. 3). In detail, total PWV and distal descending AD correlated with peak systolic strain rate ( $R = 0.42$ ,  $p < 0.001$  and  $R = -0.46$ ;  $p < 0.001$ , respectively) and peak diastolic strain rate ( $R = -0.48$ ,  $p < 0.001$  and  $R = 0.38$ ;  $p < 0.001$ , respectively). Further, AD correlated with age ( $R = -0.69$ ;  $p < 0.001$ ) and disease activity. Furthermore, peak systolic strain rate ( $R_s = 0.31$ ;  $p = 0.01$ ) and diastolic strain rate ( $R_s = -0.32$ ;  $p = 0.01$ ) and also



**Fig. 2.** Systolic strain rate and diastolic strain rate and measures of vascular stiffness in RA patients, RA patients with CVRFs, normal controls, and controls with CVRFs. A. Peak systolic mid SA circumferential strain rate; B. Peak diastolic mid SA circumferential strain rate; C. Ascending aortic distensibility; D. Proximal descending aortic distensibility; E. Distal descending aortic distensibility; and F. Total aortic pulse wave velocity. NS, not statistically significant (the mean difference is significant at the  $<0.05$  level). P values obtained after Bonferroni correction. Circle indicates mean value and the error bars indicate the 95% confidence interval.

the distal descending AD ( $R_s = -0.29$ ;  $p = 0.02$ ) correlated with disease activity.

On multivariate regression analysis, controlling for hypertension, smoking, BMI  $>30$  kg/m<sup>2</sup>, diabetes, and hyperlipidemia, peak systolic strain rate (0.04 [0.01–0.06];  $p = 0.09$ ) and peak diastolic strain rate were associated with age ( $-0.47$  [ $-0.87$ – $0.18$ ];  $p = 0.02$ ; Table 3). Further, peak diastolic strain rate was associated with RA disease activity ( $-3.90$  [ $-7.29$ – $0.51$ ];  $p = 0.03$ ), AD (3.11 [0.81–6.73];  $p = 0.01$ ) and PWV ( $-1.60$  [ $-2.82$ – $0.38$ ];  $p = 0.01$ ). AD was also inversely related to increasing age ( $-0.01$  [ $-0.02$ – $0.00$ ];  $p = 0.04$ ).

#### 4. Discussion

In this study, we used CMR to assess myocardial and vascular structure and function in RA patients with no known CVD symptoms. Our data show that, while there is no difference in overall LV systolic function (ejection fraction), size, and mass between RA patients and matched controls, regional function assessed by strain imaging is impaired in RA. Similarly, vascular function, assessed by AD and PWV, is abnormal in RA patients. Interestingly, derangements in both myocardial deformation and vascular elasticity are most severe in RA patients with CVRFs. RA patients with no

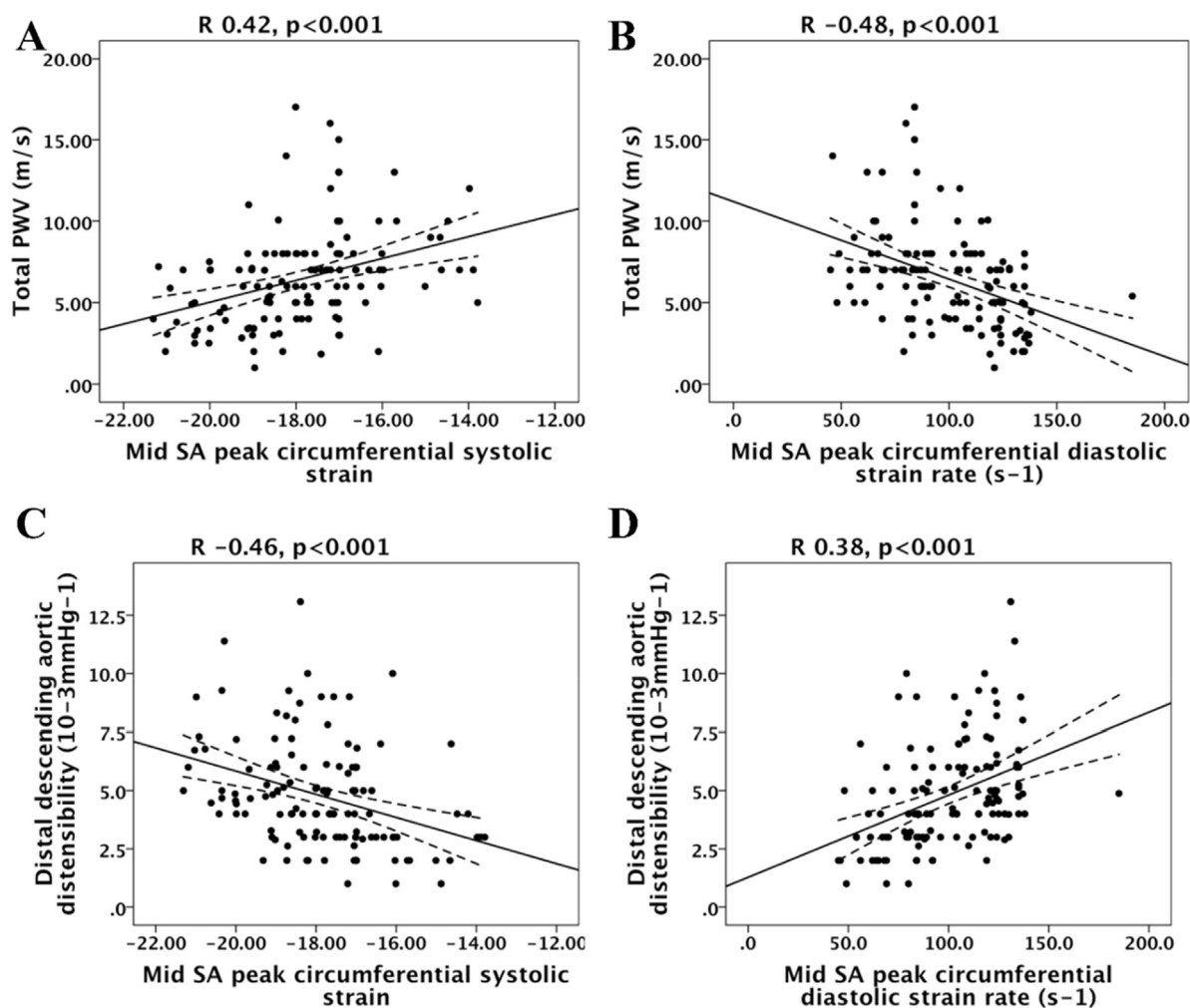


Fig. 3. Functional correlates of vascular stiffness and myocardial function. Pearson bivariate correlation between pulse wave velocity and peak systolic strain rate (A) and peak diastolic strain rate (B); and Pearson bivariate correlation between distal descending aortic distensibility and peak systolic strain rate (C) and peak diastolic strain rate (D).

CVRFs and controls with CVRFs both show an intermediate phenotype for myocardial and vascular function. Finally, we show that impaired vascular function in RA correlates with disease activity and impaired myocardial strain. These data may have implications for the clinical care of patients with RA, showing there is significant cardiovascular involvement even in asymptomatic patients, which is worsened by presence of CVRFs. Moreover, these data suggest that early identification of cardiovascular involvement in RA, with sensitive non-invasive imaging techniques like CMR, may permit earlier intervention, thus potentially reducing the effect of CVD on RA morbidity and mortality.

There is conflicting evidence in the literature regarding LV function and mass in patients with RA. In a previous report, we did not find any differences in LV function, chamber size, and mass between RA patients and matched controls.<sup>12</sup> Similarly, in this study, we found no differences in LV volumes, function, and mass between RA patients and matched controls, even in those RA patients with the most severe aberrations of myocardial and vascular function. In contradistinction, Giles *et al* reported normal myocardial structure and function in RA patients, but found slightly lower myocardial mass in RA patients when compared to controls.<sup>19</sup> Echocardiographic studies have reported inconsistent results with some investigators finding reduced<sup>9</sup> or normal systolic function,<sup>20,21</sup> or even increased LV mass in RA subjects compared to controls.<sup>22</sup>

Adding further support to the concept of subclinical involvement in asymptomatic RA patients, a speckled tracking echocardiography study by Sitia and colleagues demonstrated that LV peak systolic longitudinal and radial strains were abnormal in 22 RA patients without known CVD when compared to matched controls.<sup>21</sup> The same study also showed evidence of diastolic dysfunction in RA patients without cardiovascular dysfunction, as assessed by tissue Doppler imaging. Similarly, peak systolic longitudinal, circumferential, and radial strains were found to be abnormal in 46 RA patients when compared to controls and that chronic inhibition of interleukin-1 improved these deformational abnormalities in RA.<sup>20</sup> In a different study of 87 RA patients, global longitudinal LV and RV strain was reported to be reduced in patients when compared with healthy controls, and strain abnormalities correlated with RA disease severity.<sup>23</sup> In this study, we found left atrial size to be increased in patients with RA and in those with CVRFs. There is a tight interrelationship between left atrial size and function and myocardial performance throughout the cardiac cycle.<sup>24,25</sup> We have also shown, using CMR, that peak systolic circumferential strain and peak diastolic strain rate are both impaired in RA patients, and that the degree of impairment is worst in those RA patients with CVRFs. We hypothesize that abnormal strain reflects diastolic dysfunction from both focal and diffuse myocardial fibrosis, as we have previously demonstrated that strain abnormalities in RA correlate with left atrial size, native T1 values,

**Table 3**  
Linear regression analysis of determinants of vascular stiffness and myocardial function

	Variable	Univariate regression		Multivariate regression*	
		B (95% CI)	P value	B (95% CI)	P value
Peak systolic SA circumferential strain rate (model 1)	Age	0.35 (0.01; 0.60)	0.008	0.04 (0.01; 0.06)	0.09
	Duration of disease	0.26 (0.01; 0.61)	0.12		
	CRP	0.02 (0.01; 0.04)	0.06		
	DAS28-CRP	0.30 (0.10; 0.50)	0.003		
	LA size	0.51 (0.02; 1.03)	0.05		
	AA distensibility	-0.34 (-0.12; -0.08)	0.02		
	PDA distensibility	-0.21 (-0.42; 0.03)	0.05		
	DDA distensibility	-0.15 (-0.31; 0.01)	0.05		
	PWV	0.11 (0.03; 0.18)	0.005		
	Peak diastolic SA circumferential strain rate (model 2)	Age	-0.24 (-0.66; 0.15)		
Duration of disease		-0.01 (-0.53; 0.51)	0.97		
CRP		-0.31 (-0.55; 0.07)	0.006		
DAS28-CRP		-5.76 (-8.70; -2.82)	<0.001		
LA size		-5.50 (-13.69; 2.69)	0.18		
AA distensibility		5.82 (0.97; 8.37)	<0.001		
PDA distensibility		3.12 (-0.20; 6.43)	0.06		
DDA distensibility		2.89 (0.57; 5.21)	0.02		
PWV		-1.83 (-2.97; -0.69)	0.002		
Distensibility (model 3)		Age	-0.03 (-0.04; -0.02)	<0.001	-1.60 (-2.82; -0.38)
	Duration of disease	-0.01 (-0.02; 0.02)	0.32		
	CRP	-0.01 (-0.96; 0.01)	0.17		
	DAS28-CRP	-0.01 (-0.14; 0.04)	0.31		
	LA size	-0.16 (-0.07; 0.01)	0.02		
	AA distensibility	1.31 (-0.02; 2.65)	0.05		
	PDA distensibility	-0.01 (-0.02; 0.00)	0.04		
	DDA distensibility				
	PWV				
	PWV (model 4)	Age	0.15 (0.09; 0.21)	<0.001	
Duration of disease		0.17 (0.09; 0.25)	<0.001		
CRP		0.07 (-0.05; 0.06)	0.81		
DAS28-CRP		0.18 (-0.36; 0.72)	0.51		
LA size		1.40 (0.07; 2.72)	0.04		

AA, ascending aorta; BMI, body mass index; CRP, C-reactive protein; CI, confidence interval; DAS28-CRP, rheumatoid arthritis disease activity index, incorporating a 28 joint count and serum CRP; DDA, distal descending aorta; LA, left atrium; PDA; proximal descending aorta; PWV, pulse wave velocity; SA, short axis.

\* Stepwise regression analysis controlling for hypertension, smoking, BMI > 30 kg/m<sup>2</sup>, diabetes, and hyperlipidemia.

and extracellular volume expansion.<sup>12</sup> We found that abnormalities in strain were associated with vascular stiffness parameters, advancing age and RA disease activity. Our findings suggest that CMR may potentially be a sensitive non-invasive tool for risk stratification in patients with RA and also important for early identification of patients with myocardial involvement, before overt LV dysfunction and symptoms develop.

We show that vascular function is abnormal in RA patients without symptomatic cardiovascular disease. In a Korean study of 262 RA patients, arterial stiffness was found to correlate with age and systolic blood pressure, but not with disease-related factors.<sup>26</sup> A study of 77 RA patients found evidence of increased arterial stiffness, which correlated with age, mean arterial pressure, and C-reactive protein (CRP).<sup>7</sup> To the best of our knowledge, however, the relationship between aortic stiffness and sophisticated parameters of LV systolic and diastolic function has not been explored before in an RA population. Indeed, we show that both AD and PWV correlate with both systolic strain rate and diastolic strain rate. Furthermore, we demonstrate that aortic stiffness was associated with RA disease activity. These observations provide insights into a plausible mechanistic association between disease activity and chronic/episodic inflammation in RA with consequent vascular and myocardial inflammation and fibrosis. These interesting observations in RA cardiovascular pathobiology will need to be validated in larger cohorts.

This study is limited by its cross-sectional design, which does not permit inference of cause and effect. Second, we had relatively small numbers in some of the groups; however, despite this limitation, significant differences are observed between the 4 groups studied. Despite these limitations, we have achieved our aim of using CMR to study myocardial function and vascular stiffness in RA patients with and without cardiovascular risk factors (CVRFs) and have found interesting and novel results. CMR is potentially a

powerful tool for study of the preclinical phenotype of cardiovascular involvement in patients with RA.

## 5. Conclusions

We performed combined myocardial and vascular functional assessment with CMR in RA patients and found evidence of abnormal strain and vascular function, which is worse in older RA patients with CVRFs. Additionally, vascular stiffness in RA correlates with disease activity and impaired myocardial strain rate. In the future, a comprehensive, non-invasive, multiparametric CMR examination may be important for early detection of CVD, risk-stratification, and monitoring efficacy of therapeutic interventions in RA patients.

## Conflicts of interest

None.

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